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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/401,004	09/21/1999	HENGYUAN LANG	053904-0105	4060

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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/401,004	LANG ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-88* is/are pending in the application.

4a) Of the above claim(s) *84-87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-83 and 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/3/06 has been entered. Applicants canceled all pending claims and added new claims 72-88. Claims 84-87 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species (e.g., see 7/3/06 response, page 14, second to last paragraph, "[c]laims 72-83 and 88 are readable on the elected species"). Therefore, claims 72-83 and 88 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are withdrawn in view of Applicants' cancellation of all pending claims.

New Rejections and/or Objections

Specification

3. A substitute specification excluding the claims is required pursuant to 37 CFR § 1.125(a) because the vast majority of the specification is illegible. The font is "too light" to be readable. For example, page 28, line 1 reads -- The terms "C to C substituted phenylalkyl"-- instead of --

The terms "C_7 to C_{18} substituted phenylalkyl" (i.e., the numbers "7" and "18" are missing). This problem is pervasive throughout the specification as filed and amended (e.g., see 2/12/03 and 1/29/02 amendments).

A substitute specification must not contain new matter. The substitute specification must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strikethrough except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strikethrough cannot be easily perceived. An accompanying clean version (without markings) and a statement that the substitute specification contains no new matter must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 72-83 and 88 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description"

Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

Applicants' claims are directed to a broad genus of compounds with the formulas shown in independent claims 72 and 88. The claims encompass virtually an infinite number of compounds because all R^{1-8} positions can be independently varied with an enormous number of substitutes. For example, the permutations of the C_1 to C_{12} alkyl alone at the R^1, R^2 and R^4 positions would constitute an astronomical number of possibilities (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.), which can all be varied independently (and this represents only one substitution). In addition, the claims encompass various ring systems included saturated, unsaturated, with or without heteroatom, etc. In addition, the ring systems can be at least as large as 11 members. For example, a C_{12} substituted heterocycloalkyl would have an 11 membered heterocycle when the alkyl portion contains only 1 carbon atom (e.g., see R1, R2 and R4 Markush in claim 72). Furthermore, small rings like 4-membered heterocycles are also claimed. In addition, the positions for attachment at the R_{1-8} positions have not been specified. Thus, a furan ring, for example, could be bonded to the benzimidazole via the carbon, oxygen or some other substitution that is bound to the furan (e.g., see claim 72, R^1, R^2 and R^4 Markush listing, substituted heterocyclic ring entry).

In contrast, Applicants disclose only one synthetic scheme for producing a library of benzimidazoles (e.g., see figure 1). Using this scheme benzimidazoles are produced that contain only R^3, R^5 and R^6 substitutions (i.e., R^1, R^2, R^4 are always hydrogen).

Consequently, benzimidazoles with substituents (other than hydrogen) at positions R1, R^2 and R^4 have not been tested for biological activity. Furthermore, Applicants do not disclose large (e.g., 9, 10, 11, 12 membered) or small (e.g., 4 membered) rings at any of the R^{1-8} positions. Consequently, benzimidazoles with 4, 9, 10, 11 and 12 membered rings have not been tested for biological activity.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because a large number of substituents can be independently varied leading to virtually an infinite number of compounds (see above). Thus, Applicants have failed to disclose a "representative" number of species/examples because Applicants have failed to disclose benzimidazoles with substituents at the R^1, R^2 and R^4 positions other than hydrogen. In addition, Applicants have failed to disclose imidazoles with 4, 9, 10, 11 and 12 membered rings as currently claimed. Consequently, the aforementioned compounds have not been tested for biological activity. Furthermore, Applicants have not provided a

"general synthetic scheme" for producing all of these compounds. Therefore, the teachings in Applicants' specification are not "representative" of this enormous genus.

Furthermore, the general knowledge and level of skill in the art do not supplement the omitted description because the art is unpredictable and/or unachievable. For example, Luning (Luning, U. "Synthesizing macrocycles under thermodynamic control – dynamic combinatorial libraries and templates" *J. of Incl. Phen. Macr. Chem.* **2004**, *49*, 81-84) teach that large rings (e.g., the 9, 10, 11 and 12 membered rings currently claimed, see above) and small rings (e.g., the currently claimed 4 membered ring, see above) are particularly difficult to synthesize (e.g., see Luning, page 81, column 1, paragraph 1, "In contrast to the formation of five- or six-membered rings, cyclic organic compounds of other sizes are more difficult to synthesize. Due to ring strain, small rings and medium size rings are less stable than five- or six-membered rings, and thus they are more difficult to obtain … Entropic reasons make it more difficult to synthesize large rings because the remote ends of a long chain (A and B) have to find each other [e.g., 10, 11, 12 membered rings]"). In addition, no generally accepted method for producing all of these claimed compounds. Furthermore, many of the currently claimed compounds have not been tested for biological activity and Silverman (Silverman, Richard B. The Organic Chemistry of Drug Design and Drug Action. New York: Academic Press, Inc. **1992**, pages 19-23, especially Table 2.2) teaches that a person of skill in the art would not expect them to exhibit such activity. For example, Applicants have shown that hydrogen at the R^4 position will exhibit biological activity (e.g., see Examples wherein all of the compounds listed have a hydrogen at the R4 position). However, Silverman states that

only "fluorine" would be expected to show similar biological activity with hydrogen (e.g., see Silverman, Table 2.3, entry 11), not the infinite number of currently claimed substituents. It is well settled that claiming only a result (e.g., benzimidazole compounds with an infinite number of substituents at the R_1-R_8 positions) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor (i.e., one synthetic scheme for making a benzimidazole library), so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

5. Claims 72-83 and 88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for benzimidazoles with R^1, R^2 and R^4 = hydrogen, R^3 = short alkyl or 5-8 membered rings, R^5 = 5 or 6 membered rings, R^6 = short chain alkyl, $R^{7,8}$ = hydrogen, short alkyl or 5-8 membered rings, R does not reasonably provide enablement for a virtually infinite number of substituents at those positions as currently claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Applicants' claims are directed to a broad genus of compounds with the formulas shown in independent claims 72 and 88. The claims encompass virtually an infinite number of compounds because all R1-8 positions can be independently varied with an enormous number of substitutes. For example, the permutations of the C1 to C12 alkyl alone at the R1, R2 and R4 positions would constitute an astronomical number of possibilities (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.), which can all be varied independently (and this represents only one substitution). In addition, the claims encompass various ring systems included saturated, unsaturated, with or without heteroatom, etc. In addition, the ring systems can be at least as large as 11 members. For example, a C12 substituted heterocycloalkyl would have an 11 membered heterocycle when the alkyl portion contains only 1 carbon atom (e.g., see R1, R2 and R4 Markush in claim 72). Furthermore, small rings like 4-membered heterocycles are also claimed. In addition, the positions for attachment at the R1-8 positions have not been specified.

Thus, a furan ring, for example, could be bonded to the benzimidazole via the carbon, oxygen or some other substitution that is bound to the furan (e.g., see claim 72, R1, R2 and R4 Markush listing, substituted heterocyclic ring entry).Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: For example, Luning (Luning, U. "Synthesizing macrocycles under thermodynamic control – dynamic combinatorial libraries and templates" *J. of Incl. Phen. Macr. Chem.* **2004**, *49*, 81-84) teach that large rings (e.g., the 9, 10, 11 and 12 membered rings currently claimed, see above) and small rings (e.g., the currently claimed 4 membered ring, see above) are particularly difficult to synthesize (e.g., see Luning, page 81, column 1, paragraph 1, "In contrast to the formation of five- or six-membered rings, cyclic organic compounds of other sizes are more difficult to synthesize. Due to ring strain, small rings and medium size rings are less stable than five- or six-membered rings, and thus they are more difficult to obtain … Entropic reasons make it more difficult to synthesize large rings because the remote ends of a long chain (A and B) have to find each other [e.g., 10, 11, 12 membered rings]"). In addition, no generally accepted method for producing all of these claimed compounds. Furthermore, many of the currently claimed compounds have not been tested for biological activity and Silverman (Silverman, Richard B. The Organic Chemistry of Drug Design and Drug Action. New York: Academic Press, Inc. **1992**, pages 19-23, especially Table 2.2) teaches that a person of skill in the art would not expect them to exhibit such activity. For example, Applicants have shown that hydrogen

at the R^4 position will exhibit biological activity (e.g., see Examples wherein all of the compounds listed have a hydrogen at the R4 position). However, Silverman states that only "fluorine" would be expected to show similar biological activity with hydrogen (e.g., see Silverman, Table 2.3, entry 11), not the infinite number of currently claimed substituents.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants disclose only one synthetic scheme for producing a library of benzimidazoles (e.g., see figure 1). Using this scheme benzimidazoles are produced that contain only R3, R5 and R6 substitutions (i.e., R1, R2, R4 are always hydrogen). Consequently, benzimidazoles with substituents (other than hydrogen) at positions R1, R2 and R4 have not been tested for biological activity. Furthermore, Applicants do not disclose large (e.g., 9, 10, 11, 12 membered) or small (e.g., 4 membered) rings at any of the R1-8 positions. Consequently, benzimidazoles with 4, 9, 10, 11 and 12 membered rings have not been tested for biological activity.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as

broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided enough working examples/species that would teach this enormous and unpredictable genus. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Claims Rejections - 35 U.S.C. 102

6. Claim 88 is rejected under 35 U.S.C. 102(b) as being anticipated by Barton et al (EP 448206) (Date of Patent is **1992**) (of record).

For ***claim 88***, Barton et al (see entire document) disclose 5-[2-chloro-6-fluoro-4-(trifluoromethyl)phenoxy]-2-(trifluoromethyl)-1-Benzimidazole-1-acetamide (see Barton et al, abstract; see also attached sheet with registry number 138031-97-7P; Table 4, compound 73), which anticipates the claimed invention. This compound reads on the instant claims when R^1, R^2 and R^4 are hydrogen; R^3 is a "C_7 to C_{18} substituted phenylalkyl" (i.e., the methyl group is a "C_1 alkyl" and the ring is a "C_6 phenyl" giving "C_7 phenylalkyl" said phenylalkyl is further "substituted with O, F, Cl and is bound to the R^3 position via the "O" substitution, which represents an "oxo" or, alternatively, a "hydroxyl" substitution as denoted in the specification and page 28, paragraph 1); R^5 is a substituted C_1 alkyl (i.e., the $-CF_3$); R^6 is methylene; R^7 and R^8 are both hydrogen.

7. Claims 72-74, 77, 78 and 82 are rejected under 35 U.S.C. 102(b) as being anticipated by Teuber et al (WO 98/17651) (Date of Patent is **April 30, 1998**) (of record).

For ***claim 72, 73 and 82***, Teuber et al (see entire document) disclose, for example, N,N-diethyl-4-[3-[5-(3-furanyl)-1H-benzimidazole-1-yl]phenyl]-1-piperazineacetamide (see page 13, line 10; see also page 31, entry $3i_4$; see also page 77, line 12, registry number is 206878-30-0; other compounds also fall within the scope of the invention including compound 4d4 on page 32 wherein a methoxycarbonyl group replaces the furan ring at the R^3 position), which anticipates the claimed invention. This compound reads on the instant claims when R^1, R^2 and R^4 are hydrogen; R^3 is a furan (e.g., heterocyclic ring); R^5 is hydrogen; R^6 is -D-W-E- wherein D is absent, W is phenylene, E is piperazine substituted with a $-CH_2-$ group (e.g., C_1 to C_{12} heterocycloalkylene or, alternatively, C_5 to C_7 substituted cycloalkenylene wherein the substitution is the CH_2 group); R^7 and R^8 are both ethyl (i.e., C_1 to C_{12} alkyl).

For ***claims 74, 77, 78***, Teuber et al. disclose, for example, compound $4d_4$ (e.g., see page 32, Table 4) with the exact same substituents as that noted above for compound $3i_4$ (e.g., see page 31) with the exception that an MeO-(C=O)- group replaces the furan ring. This MeO-(C=O)- group reads on the currently claimed $-C(O)R_{11}$ wherein R_{11} is a C_1 to C_{12} substituted alkyl with an "O" substitution or, alternatively, a C_1 to C_{12} alkoxy group.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
September 11, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER